

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**



(19) Eur päisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number: 0 361 928 B1

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 27.04.94 (5) Int. Cl. 5: A61K 9/107, A61K 47/10,  
A61K 47/24  
(21) Application number: 89309901.0  
(22) Date of filing: 28.09.89

### (54) Emulsified composition.

(30) Priority: 29.09.88 JP 245120/88

(43) Date of publication of application:  
04.04.90 Bulletin 90/14

(45) Publication of the grant of the patent:  
27.04.94 Bulletin 94/17

(84) Designated Contracting States:  
CH DE ES FR GB IT LI NL SE

(56) References cited:

|                 |                 |
|-----------------|-----------------|
| EP-A- 0 171 084 | EP-A- 0 211 258 |
| EP-A- 0 257 454 | EP-A- 0 315 079 |
| FR-A- 2 455 888 | US-A- 4 835 002 |

DERWENT FILE SUPPLIER WPIL, 1989, accession no. 89-204085 [28], Derwent Publications Ltd, London, GB; & JP-A-1 143 834 (TAISHO PHARMACEUT.)

PHARMAZIE IN UNSERER ZEIT, vol. 12, no. 2, 1983, pages 55-60, Verlag ChemieGmbH; C. BEYER et al.: "Mikroemulsionen"

(73) Proprietor: SHISEIDO COMPANY LIMITED  
5-5 Ginza 7-chome  
Chu -ku Toky 104(JP)

(72) Inventor: Nakajima, Hideo c/o Shiseido Laboratories

1050, Nippa-cho  
Kohoku-ku  
Yokohama-shi  
Kanagawa(JP)

Inventor: Kohchi, Miyuki c/o Shiseido Laboratories

1050, Nippa-cho  
Kohoku-ku  
Yokohama-shi  
Kanagawa(JP)

Inventor: Tomomasa, Satoshi c/o Shiseido Laboratories

1050, Nippa-cho  
Kohoku-ku  
Yokohama-shi  
Kanagawa(JP)

(74) Representative: Hale, Stephen Geoffrey et al

J.Y. & G.W. Johnson  
Furnival House  
14/18 High Holborn  
London WC1V 6DE (GB)

EP 0 361 928 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

**Description**

The present invention relates to an emulsified composition. More specifically, it relates to an emulsified composition suitable for use as a preparation for parenteral administration.

5 Various emulsified compositions have been used in the field of, for example, pharmaceutical preparations and quasi-drug. For example, a fat emulsion for intravenous injection, which is a dispersion of lipid spheres with an average particle size of about 0.2  $\mu\text{m}$  dispersed in an aqueous phase, is already known in the art. This emulsion is usually formed by emulsifying a vegetable oil with lecithin as the emulsifier, using a high pressure homogenizer, and is utilized for a nutrient supplementation of patients or as the preparation 10 for a parenteral administration of a lipid-soluble drug. Particularly, it is effective as the preparation for an intravenous injection of a lipid-soluble drug, which usually cannot be intravenously injected as an aqueous solution, and is utilized as a drug delivery system.

Recently, passive or active oriented drug delivery systems using microspheres have been studied, it has been found that particles of 0.100 to 2.000  $\mu\text{m}$ , when administered intravenously, intraarterially or 15 intraperitoneally, are rapidly taken in from the blood stream by macrophages of the reticuloendothelial system, to become localized in lysosomes of Kupffer cells of the liver, and that particles of 0.050  $\mu\text{m}$  or less are considered to permeate through the liver endothelial system and accumulate at tumor tissues (Pharmacy International 2 (3) 1984). From such a standpoint, the above lipid emulsion for an intravenous injection with an average particle size of 0.2  $\mu\text{m}$ , which has a particle size readily taken into the 20 reticuloendothelial system, particularly the liver, is not satisfactory as the preparation for a parenteral administration of a lipid-soluble drug, and therefore, it is very important in pharmaceutical preparation to be able to prepare particles of 0.050  $\mu\text{m}$  or less which can be parenterally administered. The above-mentioned lipid emulsion for intravenous administration is known as an emulsion which can be parenterally administered, but in the system of this lipid emulsion, it is very difficult to prepare particles of 0.050  $\mu\text{m}$  or less 25 which can be parenterally administered, namely nanolipid spheres, and thus further research must be made into this problem.

It has been proposed in EP-A-211258 to provide a micro emulsion composition for parenteral administration, the composition consisting essentially of a discontinuous droplet phase comprising a pharmaceutically acceptable lipid and/or lipophilic drug and containing from 0.6 to 10% by weight of a 30 pharmaceutically acceptable emulsifier as the sole emulsifier in the composition in a sterile, non-pyrogenic aqueous continuous phase, the droplet phase having a droplet size such that less than 1% of the droplets have diameters greater than 0.125  $\mu\text{m}$ .

The present invention seeks to eliminate disadvantages of the prior art and to provide a stable emulsified composition in which lipid spheres having an average particle size of 0.010 to 0.070  $\mu\text{m}$  are 35 dispersed in an aqueous phase.

In accordance with the present invention, there is provided an emulsified composition having an average particle size of 0.010 to 0.070  $\mu\text{m}$  comprising at least the following components (A), (B) and (C):

(A) a lipid-soluble drug and a lipid;  
 (B) glycerol and water;  
 40 (C) a phospholipid and/or water-soluble nonionic surfactant having a molecular weight of 1000 or more, with (A)/(C) being 0.5 to 5 (weight ratio).

Preferably, the weight ratio of glycerol/water during emulsification is 3/7 to 9/1.

In EP-A-315079, which forms part of the state of the art in relation to the present invention only in respect of DE and SE there is disclosed in Example 3 a composition comprising 100 mg triolein, 100 mg of 45 yolk lecithin, 4 mg of Dexamethasone palmitate and 10 ml of 0.24 M glycerin aqueous solution (about 2.21% glycerol by weight). In so far as DE and SE are concerned, the compositions of the present invention are required to have a glycerol content of at least an isotonic concentration.

The average particle sizes used herein are all measured by the dynamic light scattering method, specifically by a NICOMP-270 (manufactured by HIAC/ROYCO).

50 **BRIEF DESCRIPTION OF THE DRAWINGS**

The present invention will be better understood from the description set forth below with reference to the accompanying drawings, wherein  
 55 Figure 1 shows a correlation between a particle diameter and a ratio (A)/(C) when a phospholipid is used as a component (C);  
 Fig. 2 shows a correlation between a particle diameter and a ratio (A)/(C) when a phospholipid and a nonionic surfactant are used as a component (C); and

Fig. 3 shows a correlation between the concentration of glycerol and the particle diameter.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 The lipid usable in the present invention may include vegetable oils such as soybean oil, corn oil, safflower oil, cottonseed oil, and coconut oil; synthetic or semi-synthetic mono-, di-, tri-glycerides; sterols such as cholesterol and chenodeoxycholic acid; cholesterol esters such as cholestryl linoleate and cholestryl caprylate; and monoesters such as oleyl oleate, ethyl linoleate, and ethyl laurate. These lipids may be used alone or in any combination thereof.

10 Generally speaking, the smaller the number of carbon atoms of the lipid, the easier it is to dissolve the drug but the emulsion stability becomes poor. For this reason, when a mono-, di-, tri-glyceride having 33 or less carbon atoms is used, or when a monoester having 22 or less carbon atoms is used, it becomes necessary to contain a triglyceride having a number of carbon atoms of 45 or a monoester having a number of carbon atoms of 26 or more in an amount of 1% or more in the lipid. This is because, if the emulsified

15 composition is prepared by using a mono-, di-, tri-glyceride having a number of carbon atom of 33 or less or a monoester having a number of carbon atoms of 22 or less, the stability thereof with a lapse of time is poor, and thus the particle size becomes larger.

The lipid-soluble drug usable in the present invention may be any drug which can be dissolved in the above lipid, as exemplified by antitumor agents such as mitomycin, bleomycin, docosorbicin, hexamethyl-  
20 melamine, futrafur oleic acid ester, and dilauric acid ester of 5-FU; antibacterial and antifungal agents such as penicillin, erythromycin, cephalosporin, streptomycin, kanamycin, tetracycline, chloramphenicol, isoniazide, cycloserine, amphotericin B, and glyceofurbin; non-steroidal antiphlogistics such as salicylate, indomethacin, aminopirin, phenacetin, ibuprofen, frulubiprofen, ketoprofen, and diclofenac; hormone agents such as prostaglandins, and synthetic steroid; immune controllers such as cyclosporin; and lipid-soluble  
25 vitamins such as vitamin A, vitamin D, and vitamin E.

Although there are no critical limitations to the content of the lipid-soluble drug in the component (A), the lipid-soluble drug may be preferably  $1 \times 10^{-6}\%$  to 99.9% by weight, preferably  $1 \times 10^{-5}\%$  to 99.5% by weight.

The phospholipid and the water-soluble nonionic surfactant with a molecular weight of 1000 or more in  
30 the present invention function as the emulsifiers.

The phospholipid usable in the present invention may include lecithin derived from yolk lecithin, soybean lecithin, hydrogenated products thereof, phosphatidyl choline, phosphatidylethanolamine, phosphatidyl inositol, phosphatidylserine, sphingomyelin, phosphatidic acid, and phytoglycolipid, which are synthesized or separated and purified from natural products. Examples of the nonionic surfactants are  
35 polyoxyethylene (hereinafter called POE) sorbitane fatty acid esters such as POE sorbitane monooleate, POE sorbitane monostearate, and POE sorbitane trioleate; POE sorbitol fatty acid esters such as POE sorbitol monooleate, POE sorbitol pentaoleate, and POE sorbitol monostearate; POE glycerine fatty acid esters such as POE glycerol monostearate; POE fatty acid esters such as POE monooleate, POE distearate, and POE dioleate; POE alkyl ethers such as POE oleyl ether, POE stearyl ether, and POE  
40 behenyl ether; POE sterol ethers such as POE cholestanol ether and POE cholesterol ether; POE-POP block polymers; POE-POP alkyl ethers such as POE-POP cetyl ether; POE castor oil or hydrogenated oil derivatives such as POE castor oil; and polyglycerol fatty acid esters such as decaglycerine dioleate. Among the above, those with a molecular weight of 1000 or more are used. Further, the preferable molecular weight is 1500 or more, and thus particularly preferable are POE stearyl ether, POE oleyl ether,  
45 POE monostearate, POE monooleate, POE cholestanol ether, POE cholesterol ether, and POE hydrogenated castor oil derivatives.

The molecular weight of the nonionic surfactants is preferably 1000 or more. When the molecular weight is less than 1000, the stimulation or irritation to the organisms is strong and, when such nonionic surfactants are used as an injection liquid, hemolysis is likely to occur.

50 Also, the phospholipid and the water-soluble nonionic surfactant with a molecular weight of 1000 or more may be used alone or in any combination thereof. The use of the phospholipid in combination with the water-soluble nonionic surfactant is preferable. The preferable weight ratio of the phospholipid to the nonionic surfactant is 9.5/0.5 to 1/9, more preferably 9/1 to 2/8.

The particle size of the emulsified composition according to the present invention is 0.010 to 0.070  $\mu\text{m}$ ,  
55 preferably 0.050  $\mu\text{m}$  or less, more preferably 0.040  $\mu\text{m}$  or less.

The particle size of the emulsified composition in the present invention depends on the weight ratio of (A) and (C), and the particle size tends to become smaller as the (A)/(C) ratio is lowered. Therefore, if this ratio exceeds 5, an emulsified composition with an average particle size of 0.07  $\mu\text{m}$  or less cannot be

obtained, and to obtain an emulsified composition with an average particle size of 0.050  $\mu\text{m}$  or less, which is the preferable particle size, the ratio must be 3 or less.

The administration of a large amount of a surfactant functioning as the emulsifier is not preferable, as it has an adverse affect on the blood system or blood. Accordingly, it is important to obtain small particles with as little an amount of a surfactant as possible, and therefore, the preferable ratio is 1.0 or more.

In the present invention, the weight ratio of (A)/(C) is 0.5 to 5, preferably 1.0 to 3.0.

In the present invention, the weight ratio of glycerol/water during emulsification is preferably 3/7 to 9/1, more preferably 1/1 to 8/2.

If the weight ratio of glycerol/water during emulsification is lower than 3/7, the effect of the addition thereof will not be exhibited, but if larger than 9/1, the expected effect of making the particle size smaller can not be obtained.

Although there are no critical limitation to the contents of the components (A), (B), and (C) in the present composition, the contents (A), (B), and (C) are preferably 1% to 40% by weight, 40% to 95% by weight, and 0.5% to 20% by weight.

The average particle size of the emulsified composition obtained by the present invention is 0.010 to 0.070  $\mu\text{m}$ .

Also, in the present invention, by effecting the emulsification by an emulsifying machine capable of providing a strong shearing force, such as a high pressure homogenizer or sonication emulsifying machine, lipid spheres with particle sizes of 0.050  $\mu\text{m}$  or less can be obtained.

For example, when preparing an emulsified composition with an (A)/(C) of 3, when emulsification is effected without an addition of glycerol, it is very difficult to obtain lipid spheres with particle sizes of 0.100  $\mu\text{m}$  or less, even if the emulsification conditions of a high pressure homogenizer are variously changed, and impossible to obtain lipid spheres with particle sizes of 0.070  $\mu\text{m}$  or less. When, however, emulsification is effected at a weight ratio of glycerol/water during emulsification of 3/7 to 9/1, lipid spheres with particle sizes of 0.050  $\mu\text{m}$  or less can be obtained. Further, in the case of an (A)/(C) of 1, when glycerol is not used, it is very difficult to obtain lipid spheres with particles sizes of 0.070  $\mu\text{m}$  or less, and impossible to obtain lipid spheres with particles sizes of 0.050  $\mu\text{m}$  or less. When, however, emulsification is effected at a weight ratio of glycerol/water during emulsification of 3/7 to 9/1, lipid sphere with particle sizes of 0.020  $\mu\text{m}$  or less can be obtained.

When a high pressure homogenizer is employed, preferably emulsification is effected under a pressure of 200 atm. or more, more preferably at a temperature of 70 °C or lower under a pressure of about 29,500 kPa (300 atm.) or higher when obtaining particles of 0.050  $\mu\text{m}$  or less. To obtain smaller particles, the emulsification is preferably effected at a temperature of 50 °C or less under a pressure of about 49,000 (500 atm) or more.

The emulsified composition can be diluted, by an addition of water, to a desired glycerol concentration before use. The glycerol concentration in the present invention is an isotonic concentration or more, although it may be varied depending upon the intended use thereof.

The emulsified composition of the present invention can also formulate, in addition to the essential components, various parenterally administratable components within the range which does not impair the effect of the present invention. As the aqueous phase components included among such components, are amino acids and related compounds, electrolytes, and water-soluble vitamins.

As explained above, whereas, only fine particles with an average particle size of a micro-order can be obtained in the prior art, stable ultra-fine particles of a nano-order can be obtained in the present invention.

Lipid nanospheres in such an emulsified composition, particularly those having particle sizes of 0.050  $\mu\text{m}$  or less, when administered intravenously, intraarterially or intraperitoneally, are considered to pass through the reticuloendothelial system and accumulate at the tumor tissues, and the composition can be utilized as a novel and effective preparation for parenteral administration, and as a drug delivery system of an antitumor agent etc.

As described in detail above, according to the present invention, an emulsified composition having stable lipid nanospheres with an average particle size of 0.010 to 0.070  $\mu\text{m}$  dispersed in an aqueous phase can be obtained by formulating the lipid-soluble drug and the lipid, glycerol and water, the phospholipid and/or the water-soluble nonionic surfactant having a molecular-weight of 1000 or more.

#### Examples

55

The present invention will now be further illustrated by the following Examples, wherein all parts and percentages are expressed on a weight basis unless otherwise noted.

Correlation between (A)/(C) and Average Particle Diameter

First, the correlation between the weight ratio of the lipid-soluble drug and lipid to the phospholipid and/or water-soluble nonionic surfactant having a molecular weight of 1000 or more and the average particle diameter will now be explained.

The formulation during emulsification was adjusted as shown in Table 1 and treated 30 times in a high pressure homogenizer under an emulsification pressure of about 88,300 kPa (900 atm). The average particle size of the resultant emulsified product was determined. The formulation amount listed in Table 1 is % by weight.

10

Table 1

15

20

| (A)/(C)<br>Ratio | (A) | (C) | 60% Aqueous<br>Glycerol Solution |
|------------------|-----|-----|----------------------------------|
| 1                | 12  | 12  | 76                               |
| 2                | 20  | 10  | 70                               |
| 3                | 24  | 8   | 68                               |
| 4                | 24  | 6   | 70                               |
| 5                | 25  | 5   | 70                               |
| 6                | 24  | 4   | 72                               |
| 7                | 28  | 4   | 68                               |

25

30

35

In Fig. 1, the correlation between (A)/(C) and the particle diameter when nonyloxycarbonyl mitomycin (NOC-MMC) 1% soybean oil solution was used as the component (A) (i.e., lipid-soluble drug and lipid) and yolk phosphatidylcholine was used as the component (C) (i.e., phospholipid). As is clear from Fig. 1, the (A)/(C) and the particle diameter are in approximate direct proportion and the particle diameter is 70 nm (0.070  $\mu$ m) when the (A)/(C) is about 5, and the particle diameter becomes too large when the (A)/(C) is further increased.

From the results shown in Fig. 1, it is clear that the ratio of (A)/(C) is closely related to the particle diameter and that the desired particle diameter of 70nm or less according to the present invention can be obtained when the ratio (A)/(C) is 5 or less. Furthermore, the particle diameter becomes smaller in approximate direct proportion to the ratio (A)/(C). Nevertheless, when the (A)/(C) is 3 or less, the linearity of the correlation between the (A)/(C) and the particle diameter is impaired and the particle diameter is not decreased in direct proportion to the decrease in the ratio (A)/(C). Accordingly, it is not efficient to decrease the particle diameter to 50 nm or less by using yolk phosphatidylcholine alone because a large amount of the yolk phosphatidylcholine must be used.

40

On the other hand, Fig. 2 shows the correlation between the (A)/(C) and the particle diameter when a 3:1 mixture of yolk phosphatidylcholine and POE (50) oleyl ether was used as the component (C). As is clear from the results shown in Fig. 2, a good linearity can be maintained even when the ratio (A)/(C) is 3 or less. Accordingly, when the preparation of particles having a diameter of 50 nm or less is desired, the use of a water-soluble nonionic surfactant having a molecular weight of 1000 or more, in addition to the phospholipid, is preferable.

45

Correlation between Ratio of Glycerol to Water and Particle Diameter

Next, the correlation between the ratio of glycerol to water and the particle diameter will now be explained.

50

A 20 parts amount of NOC-MMC 1% soybean oil solution, 10 parts of an emulsifier, and 70 parts of aqueous glycerol solution were formulated, followed by treating 30 times under an emulsification pressure of 600 atm in a high pressure homogenizer. Thus, the emulsified composition product was obtained.

55

The glycerol concentration of the above-mentioned aqueous glycerol solution were conveniently changed to determine the particle size of the resultant emulsified product.

The results are shown in Fig. 3. As is clear from the results shown in Fig. 3, when yolk phosphatidylcholine was used as the emulsifier (see solid line in Fig. 3), the desired particle diameter of 70 nm or less was obtained at a glycerol concentration of 50% or more. Furthermore, the minimum particle diameter value was obtained at a glycerol concentration of 70 to 80%. When the glycerol concentration was decreased from the minimum point, the particle diameter became rapidly larger.

Further, when a 3:1 mixture of yolk phosphatidylcholine and POE (50) oleyl ether was used as the emulsifier (as shown in the dotted line in Fig. 3), the desired particle size of 70 nm or less was obtained at a glycerol concentration of 30% or more and the minimum particle diameter value was obtained at a glycerol concentration of 70 to 80%. Accordingly, the preferable glycerol concentration is 30 to 90% and, especially when the glycerol concentration is 70 to 80%, an extremely small particle diameter can be obtained.

#### Correlation between Ratio of Phospholipid and Nonionic Surfactant and Particle Diameter

After preemulsifying 5.0% of tocopherol acetate, 15.0% of soybean oil, 10% of an emulsifier, 30% of water, and 40.0% of glycerol, the preemulsified product was treated 30 times at 50°C under a pressure of about 78,500 kPa (800 atm) by using a Microfluidizer. Thus, the emulsified product was obtained.

The composition of the emulsifier and the particle diameter are shown in Table 2.

Table 2

| Lecithin : POE (50) stearyl ether | Particle Diameter ( $\mu\text{m}$ ) |
|-----------------------------------|-------------------------------------|
| 1 : 0                             | 0.040                               |
| 0.9 : 0.1                         | 0.034                               |
| 0.75 : 0.25                       | 0.032                               |
| 0.5 : 0.5                         | 0.032                               |
| 0.25 : 0.75                       | 0.035                               |
| 0 : 1                             | 0.044                               |

As is clear from the results shown in Table 2, a finer particle size can be obtained by using a mixture of lecithin (i.e., phospholipid) and POE (50) stearyl ether (i.e., water-soluble nonionic surfactant having a molecular weight of 1000 or more), compared with the use of the lecithin or the POE (50) stearyl ether alone. Especially when the ratio of the lecithin is 75 to 50%, an extremely fine particle diameter can be obtained.

#### Examples 1 - 9

First, 1.1 parts of diclofenac, 20.9 parts of soybean oil, 28 parts of water, 41.3 parts of glycerol, and 8.7 parts of the phospholipid shown in Table 3 and/or the water-soluble nonionic surfactant having a molecular weight of 1000 or more (i.e., emulsifier) were pre-emulsified, then emulsification was effected at 50°C by a Microfluidizer (Microfluidic Co.) under the conditions of about 98,100 kPa (1000 atm.) and a 20 times treatment, and thereafter, 120 parts of water were added and the emulsion was sterilized by passing the same through a 0.22  $\mu\text{m}$  membrane filter. The particle diameters of these emulsified compositions immediately after preparation are shown in Table 3. These particles are translucent or substantially transparent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

45

50

55

Table 3

|    |    | Emulsifier  | Particle diameter ( $\mu\text{m}$ ) |
|----|----|---|-------------------------------------|
| 5  | 10 | Example 1      Purified yolk lecithin   | 0.046                               |
| 10 | 15 | 2      Purified yolk lecithin + POE 60<br>hydrogenated castor oil derivative<br>(8:2) | 0.040                               |
| 15 | 20 | 3      same as above (1:1)  | 0.040                               |
| 20 | 25 | 4      same as above (3:7)  | 0.045                               |
| 25 | 30 | 5      Hydrogenated castor oil derivative   | 0.049                               |
| 30 | 35 | 6      Purified yolk lecithin + POE 30<br>cholestanol ether (1:1)                     | 0.038                               |
| 35 | 40 | 7      POE 30 cholestanol ether   | 0.047                               |
| 40 | 45 | 8      Purified soybean lecithin  | 0.047                               |
| 45 | 50 | 9      Decaglycerine dioleate   | 0.050                               |

Comparative Examples 1 - 9

The same compositions, except that the glycerine in the recipes shown in Examples 1 - 9 was replaced with water, were similarly prepared to give Comparative examples. The particle diameters of these emulsified compositions immediately after preparation are shown in Table 2. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

Table 4

|    |                       | Emulsifier   | Particle diameter ( $\mu\text{m}$ ) |
|----|-----------------------|--|-------------------------------------|
| 10 | Comparative Example 1 | Purified yolk lecithin   | 0.101                               |
| 15 | 2                     | Purified yolk lecithin + POE 60 hydrogenated castor oil derivative (8:2) | 0.093                               |
| 20 | 3                     | same as above (1:1)  | 0.098                               |
| 25 | 4                     | same as above (3:7)  | 0.106                               |
| 30 | 5                     | Hydrogenated castor oil derivative                                       | 0.117                               |
|    | 6                     | Purified yolk lecithin + POE 30 cholestanol ether (1:1)                  | 0.092                               |
|    | 7                     | POE 30 cholestanol ether   | 0.099                               |
|    | 8                     | Purified soybean lecithin  | 0.105                               |
|    | 9                     | Decaglycerine dioleate   | 0.100                               |

35 As shown in Table 3 and Table 4, the superiority of Examples 1 - 9 formulated with glycerol according to the present invention is obvious.

#### Example 10

40 First, 15 parts of soybean oil containing 10% of 5-FU palmitate, 16 parts of water, 56 parts of glycerol, and 15 parts of POE 40 cholestanol ether were pre-emulsified, then emulsification was effected at 50°C by Manton Gaulin under the conditions of about 49,000 kPa (500 atm.) and a 30 times treatment, and thereafter, 100 parts of water were added, and the emulsion was sterilized by passing the same through a 0.22  $\mu\text{m}$  membrane filter and were transparent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

#### Example 11

50 First, 20 parts of soybean oil containing 10% of 5-FU palmitate, 16 parts of water, 56 parts of glycerol, and 10 parts of POE (40) cholestanol ether were preemulsified, then emulsification was effected at 50°C by Manton Gaulin under the conditions of about 49,000 kPa (500 atm.) and a 30 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22  $\mu\text{m}$  membrane filter. These emulsion compositions immediately after preparation had a particle diameter of 0.042  $\mu\text{m}$  and were transparent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing room temperature for 3 months, no change thereof was observed.

Example 12

First 24 parts of soybean oil containing 10% of 5-FU palmitate, 16 parts of water, 54 parts of glycerol, and 8 parts of POE 40 cholestanol ether were preemulsified, then emulsification was effected at 50°C by  
 5 Manton Gaulin under the conditions of about 49,000 kPa (500 atm.) and a 30 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. These emulsion compositions immediately after preparation had a particle diameter of 0.062 µm and were transparent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was  
 10 recognized.  
 15

As shown in the results of Examples 10 - 12, according to the present invention, it is obvious that the particle diameter is controlled by the ratio of lipid to emulsifier.

Example 13

First, 2 parts of futrafural palmitate, 1 part of soybean oil, 19 parts of ethyl oleate, 14 parts of water, 54 parts of glycerol, 5 parts of purified yolk lecithin, and 5 parts of POE 60 hydrogenated castor oil were preemulsified, then emulsification was effected at 50°C by Manton Gaulin under the conditions of about 49,000 kPa (500 atm.) and a 10 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter.

These emulsion compositions immediately after preparation had a particle diameter of 0.028 µm and were transparent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

Example 14

First, 1 part of cyclosporin, 1 part of soybean oil, 14 parts of ethyl laurate, 16 parts of water, 58 parts of glycerol, 7 parts of purified yolk lecithin, and 3 parts of POE (60) hydrogenated castor oil were preemulsified, then emulsification was effected at 50°C by Manton Gaulin under the conditions of about 49,000 kPa (500 atm.) and a 10 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. These emulsion compositions immediately after preparation had a particle diameter of 0.020 µm and were transparent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

Example 15

First, 2 parts of erythromycin, 1 part of soybean oil, 27 parts of glycerine tricaprylate, 38 parts of water, 26 parts of glycerol, 1 part of purified yolk lecithin, and 6 parts of POE (30) cholestanol ether were preemulsified, then emulsification was effected at 70°C by Microfluidizer (Microfluidics Co.) under the conditions of about 98,100 kPa (1000 atm.) and a 20 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. These emulsion compositions immediately after preparation had a particle diameter of 0.062 µm and were translucent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

Example 16

First, 24 parts of soybean oil, containing 0.001% of prostaglandin E<sub>2</sub>, 36 parts of water, 38 parts of glycerol, and 10 parts of POE (50) cholestanol ether were preemulsified, then emulsification was effected at 70°C by Microfluidizer (Microfluidics Co.) under the conditions of about 98,100 kPa (1000 atm.) and a 20 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. These emulsion compositions immediately after preparation had a particle diameter of 0.047 µm and were translucent. As a result of an evaluation of the state and the particle diameter of the emulsions after standing at room temperature for 3 months, no change thereof was observed.

Example 17

First, 25 parts of tocopherol acetate, 2 parts of soybean oil, 9 parts of purified yolk lecithin, 32 parts of water, and 32 parts of glycerol were preemulsified, then emulsification was effected at 50°C by Manton Gaulin under the conditions of about 49,000 kPa (500 atm.) and a 20 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. Further, 1050 parts of sterilized water were added thereto to obtain an isotonic liquid, i.e., vitamin E preparation for intravenous administration. The particle diameter of the preparation was 0.050 µm.

As a result of an evaluation of the state and the particle size of the emulsion after standing at room temperature for 3 months, no change thereof was observed.

Example 18

First, 0.2 parts of nonyloxycarbonyl mitomycin, 19.8 parts soybean oil, 5 parts of yolk phosphatidyl choline, 5 parts of POE (50) monostearate, 30 parts of water, and 40 parts of glycerol were preemulsified, then emulsification was effected at 50°C by Microfluidizer under the conditions of about 78,500 kPa (800 atm.) and a 30 times treatment, and thereafter, 100 parts of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. Further, 300 parts of sterilized water were added thereto to obtain nonyloxy carbonyl mitomycin C for intravenous administration. The particle diameter of the preparation was 0.32 µm.

As a result of an evaluation of the state and the particle size of the emulsion after standing at room temperature for 3 months, no change thereof was observed.

Example 19

First, 0.1 part of amphotericin B, 9.9 parts of soybean oil, 8 parts of yolk phosphatidyl choline, 2 parts of POE (30) oleyl ether, 30 parts of water, and 50 parts of glycerol were preemulsified, then emulsification was effected at 40°C by a Microfluidizer under the conditions of about 78,500 kPa (800 atm.) and a 30 times treatment, and thereafter, 100 parts by weight of water were added and the emulsion was sterilized by passing the same through a 0.22 µm membrane filter. Further, 100 parts of sterilized water were added and amphotericin B preparation for intravenous administration. The emulsified particle diameter was 0.018 µm.

As a result of an evaluation of the state and the particle size of the emulsion after standing at room temperature for 3 months, no change thereof was observed.

**Claims****Claims for the following Contracting States : CH, ES, FR, GB, IT, LI, NL**

1. An emulsified composition having an average particle size of 0.010 to 0.070 µm and comprising at least the following components (A), (B) and (C);
  - (A) a lipid-soluble drug and a lipid;
  - (B) glycerol and water;
  - (C) at least one component selected from the group consisting of phospholipids and water-soluble nonionic surfactants having a molecular weight of 1000 or more,
 the weight ratio of (A)/(C) being 0.5/1 to 5/1.
2. An emulsified composition as claimed in claim 1, wherein the weight ratio of glycerol/water in the component (B) during emulsification is 3/7 to 9/1.
3. An emulsified composition as claimed in claim 1 or 2, wherein the component (C) comprises a phospholipid and a water-soluble nonionic surfactant at a weight ratio of 9.5/0.5 to 1/9.
4. An emulsified composition as claimed in any of claims 1 to 3, wherein the contents of the components (A), (B) and (C) are 1 to 40% by weight, 40 to 95% by weight and 0.5 to 20% by weight, respectively, based on the weight of the composition.
5. An emulsified composition as claimed in any of claims 1 to 4, wherein the content of the lipid-soluble drug in the component (A) is  $1 \times 10^{-6}$  % to 99.9% by weight.

6. An emulsified composition as claimed in any of claims 1 to 5, wherein the weight ratio of (A)/(C) is 1/1 to 3/1.
7. An emulsified composition as claimed in any of claims 1 to 6, wherein the emulsification has been carried out in a high-pressure homogeniser or sonication emulsifying machine and the average particle size is 0.01 to 0.05  $\mu\text{m}$ .
8. An emulsified composition as claimed in any of claims 1 to 7, wherein component (A) comprises a mono-, di-, or tri-glyceride having more than 33 carbon atoms or a mono-, di-, or tri-glyceride monoester having more than 22 carbon atoms as lipid and an antitumor agent or antifungal agent or non-steroidal antiphlogistic or hormone or vitamin dissolved therein as lipid-soluble drug.

**Claims for the following Contracting States : DE, SE**

1. An emulsified composition having an average particle size of 0.010 to 0.070  $\mu\text{m}$  and comprising at least the following components (A), (B) and (C):
  - (A) a lipid-soluble drug and a lipid;
  - (B) glycerol and water, the concentration of the glycerol being at least an isotonic concentration;
  - (C) at least one component selected from the group consisting of phospholipids and water-soluble nonionic surfactants having a molecular weight of 1000 or more,
 the weight ratio of (A)/(C) being 0.5/1 to 5/1.
2. An emulsified composition as claimed in claim 1, wherein the weight ratio of glycerol/water in the component (B) during emulsification is 3/7 to 9/1.
3. An emulsified composition as claimed in claim 1 or 2, wherein the component (C) comprises a phospholipid and a water-soluble nonionic surfactant at a weight ratio of 9.5/0.5 to 1/9.
4. An emulsified composition as claimed in any of claims 1 to 3, wherein the contents of the components (A), (B) and (C) are 1 to 40% by weight, 40 to 95% by weight and 0.5 to 20% by weight, respectively, based on the weight of the composition.
5. An emulsified composition as claimed in any of claims 1 to 4, wherein the content of the lipid-soluble drug in the component (A) is  $1 \times 10^{-6}$  % to 99.9% by weight.
6. An emulsified composition as claimed in any of claims 1 to 5, wherein the weight ratio of (A)/(C) is 1/1 to 3/1.
7. An emulsified composition as claimed in any of claims 1 to 6, wherein the emulsification has been carried out in a high-pressure homogeniser or sonication emulsifying machine and the average particle size is 0.01 to 0.05  $\mu\text{m}$ .
8. An emulsified composition as claimed in any of claims 1 to 7, wherein component (A) comprises a mono-, di-, or tri-glyceride having more than 33 carbon atoms or a mono-, di-, or tri-glyceride monoester having more than 22 carbon atoms as lipid and an antitumor agent or antifungal agent or non-steroidal antiphlogistic or hormone or vitamin dissolved therein as lipid-soluble drug.

**Patentansprüche**

**Patentansprüche für folgende Vertragsstaaten : CH, ES, FR, GB, IT, LI, NL**

1. Emulgierte Zusammensetzung mit einer durchschnittlichen Teilchengröße von 0,010 bis 0,070  $\mu\text{m}$  und mit mindestens den folgenden Komponenten (A), (B) und (C):
  - (A) einem lipidlöslichen Arzneimittel und einem Lipid;
  - (B) Glyzerin und Wasser;
  - (C) mindestens einer Komponente, die ausgewählt ist aus der Gruppe bestehend aus Phospholipiden und wasserlöslichen nichtionogenen oberflächenaktiven Mitteln mit einem Molekulargewicht von 1000 oder darüber,
 wobei das Gewichtsverhältnis von (A)/(C) bei 0,5/1 bis 5/1 liegt.

2. Emulgierte Zusammensetzung nach Anspruch 1, in der das Gewichtsverhältnis von Glyzerin/Wasser in der Komponente (B) während der Emulgierung bei 3/7 bis 9/1 liegt.
3. Emulgierte Zusammensetzung nach Anspruch 1 oder 2, in der die Komponente (C) ein Phospholipid sowie ein wasserlösliches nichtionogenes oberflächennaktives Mittel in einem Gewichtsverhältnis von 9,5/0,5 bis 1/9 aufweist.
4. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 3, in der die Gehalte an den Komponenten (A), (B) und (C) bei 1 bis 40 Gew.-%, 40 bis 95 Gew.-% bzw. 0,5 bis 20 Gew.-%, bezogen auf das Gewicht der Zusammensetzung liegen.
5. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 4, in der der Gehalt an dem lipidlöslichen Arzneimittel in der Komponente (A) bei  $1 \times 10^{-6}$  Gew.-% bis 99,9 Gew.-% liegt.
10. 6. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 5, in der das Gewichtsverhältnis von (A)/(C) bei 1/1 bis 3/1 liegt.
15. 7. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 6, in der die Emulgierung in einem Hochdruck-Homogenisator oder in einer Ultraschall-Emulgierzvorrichtung durchgeführt wird und die durchschnittliche Teilchengröße bei 0,01 bis 0,05 µm liegt.
20. 8. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 7, in der die Komponente (A) ein Mono-, Di- oder Tri-Glyzerid mit mehr als 33 Kohlenstoffatomen oder ein Mono-, Di- oder Tri-Glyzeridmonoester mit mehr als 22 Kohlenstoffatomen als Lipid enthält sowie ein Antitumormittel oder ein Fungizid oder ein nicht-steroidales Antiphlogistikum oder Hormon oder ein Vitamin, gelöst als lipidlösliches Arzneimittel.

**Patentansprüche für folgende Vertragsstaaten : DE, SE**

30. 1. Emulgierte Zusammensetzung mit einer durchschnittlichen Teilchengröße von 0,010 bis 0,070 µm und mit mindestens den folgenden Komponenten (A), (B) und (C):
  - (A) einem lipidlöslichen Arzneimittel und einem Lipid;
  - (B) Glyzerin und Wasser, wobei die Konzentration des Glyzerins mindestens einer isotonischen Konzentration entspricht;
  - (C) mindestens einer Komponente, die ausgewählt ist aus der Gruppe bestehend aus Phospholipiden und wasserlöslichen nichtionogenen oberflächenaktiven Mitteln mit einem Molekulargewicht von 1000 oder darüber,wobei das Gewichtsverhältnis von (A)/(C) bei 0,5/1 bis 5/1 liegt.
40. 2. Emulgierte Zusammensetzung nach Anspruch 1, in der das Gewichtsverhältnis von Glyzerin/Wasser in der Komponente (B) während der Emulgierung bei 3/7 bis 9/1 liegt.
3. Emulgierte Zusammensetzung nach Anspruch 1 oder 2, in der die Komponente (C) ein Phospholipid sowie ein wasserlösliches nichtionogenes oberflächenaktives Mittel in einem Gewichtsverhältnis von 9,5/0,5 bis 1/9 aufweist.
45. 4. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 3, in der die Gehalte an den Komponenten (A), (B) und (C) bei 1 bis 40 Gew.-%, 40 bis 95 Gew.-% bzw. 0,5 bis 20 Gew.-%, bezogen auf das Gewicht der Zusammensetzung liegen.
50. 5. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 4, in der der Gehalt an dem lipidlöslichen Arzneimittel in der Komponente (A) bei  $1 \times 10^{-6}$  Gew.-% bis 99,9 Gew.-% liegt.
55. 6. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 5, in der das Gewichtsverhältnis von (A)/(C) bei 1/1 bis 3/1 liegt.
7. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 6, in der die Emulgierung in einem Hochdruck-Homogenisator oder in einer Ultraschall-Emulgierzvorrichtung durchgeführt wird und die

durchschnittliche Teilchengröße bei 0,01 bis 0,05 µm liegt.

8. Emulgierte Zusammensetzung nach einem der Ansprüche 1 bis 7, in der die Komponente (A) ein Mono-, Di- oder Tri-Glyzerid mit mehr als 33 Kohlenstoffatomen oder ein Mono-, Di- oder Tri-Glyzeridmonoester mit mehr als 22 Kohlenstoffatomen als Lipid enthält sowie ein Antitumormittel oder ein Fungizid oder ein nicht-steroidales Antiphlogistikum oder Hormon oder ein Vitamin, gelöst als lipidlösliches Arzneimittel.

**Revendications**

10 **Revendications pour les Etats contractants suivants : CH, ES, FR, GB, IT, LI, NL**

1. Une composition émulsifiée présentant une dimension particulaire moyenne de 0,010 à 0,070 µm comprenant au moins les constituants (A), (B) et (C) suivants:
  - (A) un médicament liposoluble et un lipide;
  - (B) glycérol et eau;
  - (C) au moins un constituant choisi dans le groupe comprenant les phospholipides et les agents tensioactifs non ioniques hydrosolubles dont le poids moléculaire est de 1000 ou davantage; le rapport pondéral (A)/(C) étant compris entre 0,5/1 et 5/1.
- 20 2. Une composition émulsifiée ainsi que revendiquée dans la revendication 1, dans laquelle le rapport pondéral glycérol/eau du constituant (B) durant l'émulsification est compris entre 3/7 et 9/1.
3. Une composition émulsifiée ainsi que revendiquée dans la revendication 1 ou 2, dans laquelle le constituant (C) comprend un phospholipide et un agent tensioactif non ionique hydrosoluble selon un rapport pondéral compris entre 9,5/0,5 et 1/9.
4. Une composition émulsifiée ainsi que revendiquée dans l'une quelconques des revendications 1 à 3, dans laquelle les teneurs des constituants (A), (B) et (C) sont respectivement de 1% à 40% en poids, de 40% à 95% en poids et de 0,5% à 20% en poids, exprimées par rapport au poids de la composition.
5. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 4, dans laquelle la teneur en médicament liposoluble du constituant (A) est comprise entre  $1 \times 10^{-6}\%$  et 99,9% en poids.
- 35 6. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 5, dans laquelle le rapport pondéral de (A)/(C) est compris entre 1/1 et 3/1.
7. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 6, dans laquelle l'émulsification est mise en oeuvre dans un appareil d'homogénéisation sous pression élevée ou un appareil d'émulsification par sonication et la dimension particulaire moyenne est comprise entre 0,01 et 0,05 µm.
- 40 8. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 7, dans laquelle le constituant (A) comprend un mono-, di- ou triglycéride comprenant plus de 33 atomes de carbone, ou un monoester de mono-, di- ou triglycéride présentant plus de 22 atomes de carbone, en tant que lipide, et un agent antitumoral ou agent antifongique, ou antiphlogistique non-stéroïdal ou une hormone ou une vitamine qui y est dissout en tant que médicament lipo-soluble.

60 **Revendications pour les Etats contractants suivants : DE, SE**

1. Une composition émulsifiée présentant une dimension particulaire moyenne de 0,010 à 0,070 µm comprenant au moins les constituants (A), (B) et (C) suivants:
  - (A) un médicament lipo-soluble et un lipide;
  - (B) glycérol et eau, la concentration en glycérol étant d'au moins une concentration isotonique ;
  - (C) au moins un constituant choisi dans le groupe comprenant les phospholipides et les agents tensioactifs non ioniques hydrosolubles dont le poids moléculaire est de 1000 ou davantage; le rapport pondéral (A)/(C) étant compris entre 0,5/1 et 5/1.

2. Une composition émulsifiée ainsi que revendiquée dans la revendication 1, dans laquelle le rapport pondéral glycérol/eau du constituant (B) durant l'émulsification est compris entre 3/7 et 9/1.
3. Une composition émulsifiée ainsi que revendiquée dans la revendication 1 ou 2, dans laquelle le constituant (C) comprend un phospholipide et un agent tensioactif non ionique hydrosoluble selon un rapport pondéral compris entre 9,5/0,5 et 1/9.
4. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 3, dans laquelle les teneurs en les constituants (A), (B) et (C) sont respectivement de 1% à 40% en poids, de 40% à 95% en poids et de 0,5% à 20% en poids, exprimées par rapport au poids de la composition.
5. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 4, dans laquelle la teneur en médicament soluble dans du lipo-soluble du constituant (A) est comprise entre  $1 \times 10^{-6}$  % et 99,9% en poids.
6. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 5, dans laquelle le rapport pondéral de (A)/(C) est compris entre 1/1 et 3/1.
- 20 7. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 6, dans laquelle l'émulsification est mise en œuvre dans un appareil d'homogénéisation sous pression élevée ou un appareil d'émulsification par sonication et la dimension particulaire moyenne est comprise entre 0,01 et 0,05 µm.
- 25 8. Une composition émulsifiée ainsi que revendiquée dans l'une quelconque des revendications 1 à 7, dans laquelle le constituant (A) comprend un mono-, di- ou triglycéride comprenant plus de 33 atomes de carbone, ou un monoester de mono-, di- ou triglycéride présentant plus de 22 atomes de carbone, en tant que lipide, et un agent antitumoral ou agent antifongique, ou antiphlogistique non-stéroïdal ou une hormone ou une vitamine qui y est dissout dans laquelle en tant que médicament lipo-soluble.

30

35

40

45

50

55

Fig. 1

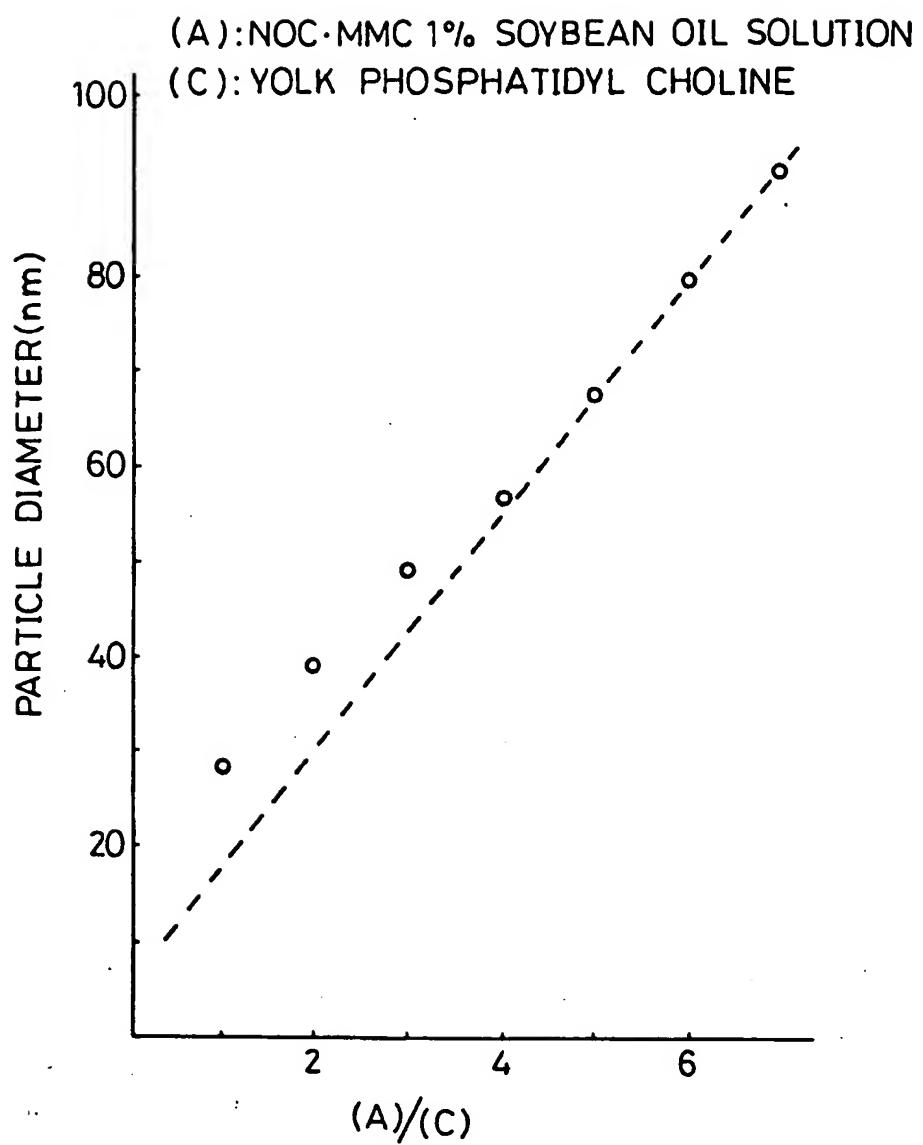


Fig. 2

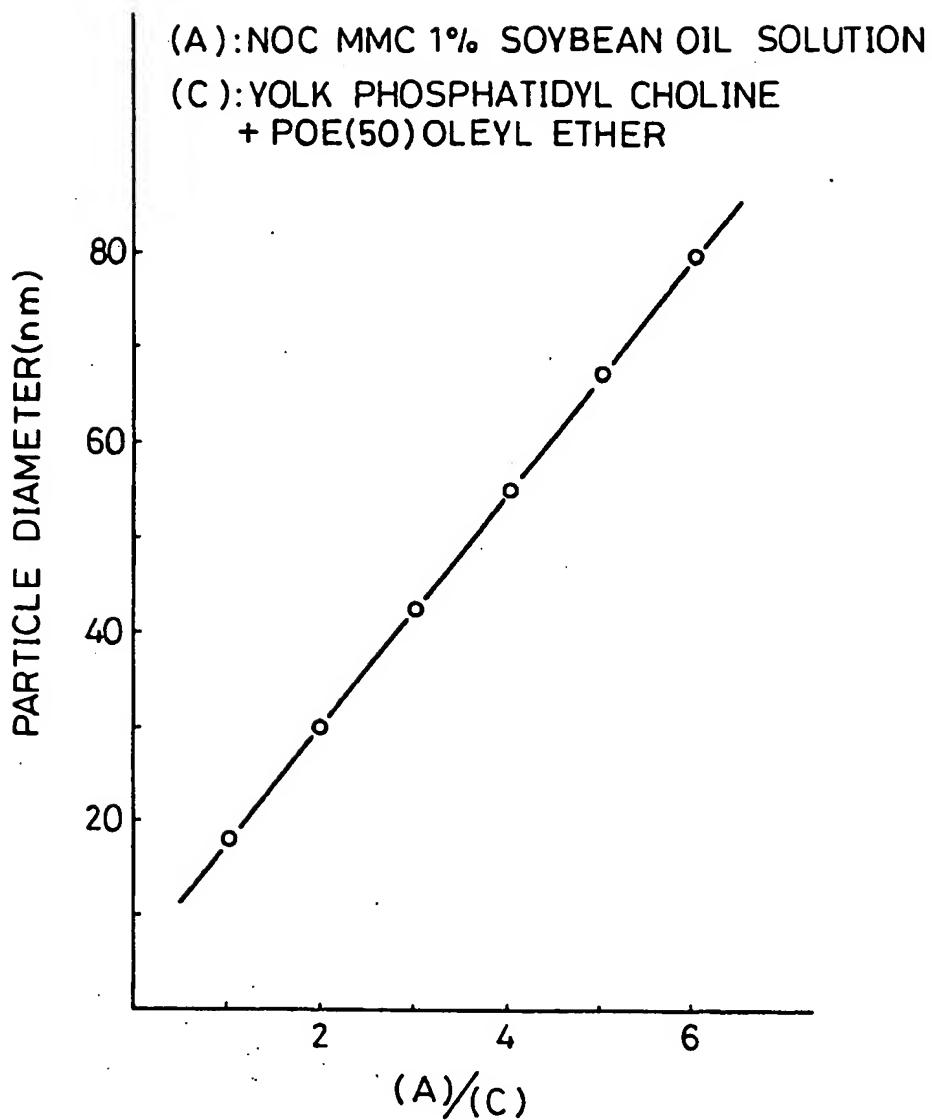


Fig. 3

